ARTICLES

Studies on Gui-Lin-Tang in the Treatment of Rheumatoid Arthritis

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ABSTRACT

Seventy-two patients with definite or classical rheumatoid arthritis were treated with Gui-Lin-Tang and 44 patients (33 females, 11 males) completed the study. Thirty-four patients were treated with Gui-Lin-Tang alone. Ten patients were treated with Gui-Lin-Tang in addition to gold or D-penicillamine. All the patients tolerated the drug and had an averaged 77.2 days follow-up. Twelve patients (27.2%) were markedly improved, 22 (50%) moderately or slightly improved, and 10 (22.8%) unimproved. IgG, IgA and IgM values were decreased in 61.5% of the patients treated with Gui-Lin-Tang alone.

Key words : Gui-Lin-Tang, Rheumatoid arthritis.

INTRODUCTION

The etiology of rheumatoid arthritis is unknown, but the pathogenesis of rheumatoid arthritis can be considered as immunological events induced by the etiological factor, and inflammatory reaction followed[1]. The detection of large numbers of T-lymphocytes in synovial and the presence of lymphokines in synovial fluid imply a role for cell-mediated immunity[2]. Nonsteroid anti-inflammatory and disease-modifying drugs like gold and D-penicillamine are mostly used singly or in combination in treatment. But for patients using these drugs there are many restrictions due to their severe adverse side effects[3,4,5].

Chinese herbal drugs have been used to treat many kinds of inflammatory disease since ancient times. Gui-Zhi-Tang, found by Chung-Ching Chang in about 1800 years ago, is a basic Chinese herb formula for acute inflammatory disease[6]. Many formulas have been developed from Gui-Zhi-Tang for treating arthritis. Gui-Zhi-Tang consists of five herbs including Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus and Glycyrrhizae

Radix. The Gui-Lin-Tang used in this study was modified by adding Aconiti Tuber, Atractylodis Rhizoma and Poria. This Gui-Lin-Tang has been shown in animal and human studies to posses analgesic, anti-inflammatory and immune modulating effects[7].

The purpose of the present study was to demonstrate the effects of Gui-Lin-Tang in patients with rheumatoid arthritis. The clinical improvements as well as certain changes in laboratory parameters, especially erythrocyte sedimentation rate and the titer of immune globulin were evaluated. The adverse side effects and toxicity were also evaluated. Our experience with Gui-Lin-Tang in the treatment of rheumatoid arthritis is presented.

EXPERIMENTAL

Materials

The preparation consisted of coarse powder of Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus, Glycyrrhizae Radix, Aconiti Tuber, Atractylodis Rhizoma, Poria in the ratio of 4:3:3:3:1.5:5:5:0.5. The drug was prepared by immersing 1 kg of the mixture in 5 L 50% alcohol and decocted in 60°C hot water bath 4 times. The extracted solutions were mixed then evaporated and concentrated in a rotary vacuum evaporator at a temperature below 50°C. The extraction rate was 22%.

Methods

All the patients admitted to this study had "definite" or "classical" rheumatoid arthritis according to American Rheumatism Association criteria and had evidence of active disease[8,9]. Most of the patients were at the early stage of the disease. Their clinical progress was assessed by the following indices: (1) duration of morning stiffness (mins), (2) numbers of painful joints, (3) numbers of swollen joints, (4) grip strength (1 b), (5) erythrocyte sedimentation rate (ESR) by the Weatergren method, and (6) immunoglobulin IgG, IgA, IgM. The first four indices were recorded weekly and the last two indices recorded monthly. For monitoring toxicity, patients were regularly questioned about skin rash, epigastralgia, edema, diarrhea, bleeding tendency and other possible side effects. Hemoglobin, white blood cell count, platelet estimate GOT, GPT, BUN, creatinine and urinalysis were monitored monthly.

Roentgenographic rheumatoid progression and functional capacity were assessed at the beginning and at the end of therapy in each patients according to American Rheumatism Association by Steinbrocker.

All patients were treated with 6 g of Gui-Lin-Tang daily, giving 2 g orally thirty minutes after each meal three times a day. There were three groups of patients in this study. One group of patients who had never been treated with antirheumatic drug were treated with Gui-Lin-Tang alone. The second group of patients who had been treated with NSAID discontinued the drug for washing out the effect of NSAID then given the Gui-Lin-Tang. The third group of patients who had higher activity and had been treated with gold and D-penicillamine in addition to NSAID because of failure of treatment by first-line drug, were treated with Gui-Lin-Tang in combination with gold or D-penicillamine.

The criteria for categorizing the response of rheumatoid activity to Gui-Lin-Tang therapy

were as follows: (1) marked improvement—clinical symptoms and signs including morning stiffness, joint pain, joint swelling, grip strength and ESR improved, (2) moderate or slight improvement—clinical symptoms and signs improved but ESR not improved and (3) unimprovement—clinical symptoms and signs as well as ESR not improved.

RESULTS

Table 1 summarizes the outcome of the Gui-Lin-Tang in the 44 patients studies. All of the markedly improved patients were female. All of the 8 patients treated with Gui-Lin-Tang in combination with gold had improvement. A 51-year-old female patient was withdrown from steroid dependence after having been treated with Gui-Lin-Tang and gold for 3 months. The mean values of eight clinical and laboratory parameters before and after treatment were shown in Table 2. Duration of morning stiffness was not applicable to all the patients. The grip strength, articular indices by numbers of painful or swollen joints and ESR were considered the most useful criteria for assessing improvement of rheumatoid activity. The grip strength mea-

Table 1. Summary of the outcome of Gui-Lin-Tang treatment in 44 patients

	Marked improvement	Moderate or slight improvement	No improvement
Gui-Lin-Tang	7	18	9
Gui-Lin-Tang +Gold	5	3	0
Gui-Lin-Tang +D-Penicillamine	0	1	1
Total	12	22	10

Table 2. Mean value of clinical and laboratory parameters pre- and post-treatment

		Morning stiffness (min)	Sum grip strength of both hands (lb)	Painful joints	Swollen joints	ESR	IgG	IgA	IgM
GLT	pre-R	150.0 ±30.0	51.8±3.3	7.79 ±0.78	5.29 ±0.73	42.3 ±7.6	1479 ±182	346 ±32	158 ±25
	post-R	84.2 ±26.8*	57.6±3.7	3.56 ±0.55***	1.50 ±0.41***	41.5 ±5.1	1382 ±185	320 ±33	142 ±22
GLT & Gold	pre-R	128.0 ±57.0	19.0±3.8	15.40 ±3.30	8.75 ±2.53	69.4 ±19.7	1330 ±250	310 ±26	152 ±15
	post-R	49.4 ±20.8	22.7±20.8	2.50 ±1.00**	1.13 ±0.58*	47.1 ±16.8	1356 ±208	278 ±25	155 ±20

(1) GLT: Gui-Lin-Tang.
(2) Mean±SE (n=34 for GLT, 8 for GLT & Gold).
(3) *$p<0.05$, **$p<0.01$, ***$p<0.001$ as analyzed by paired comparison Student's t test.

sured by hand gripper, not by sphygmomanometer, was considered sensitive if the activity and articular damage were not very severe. Most of the mean values of the parameters were shown at abnormally lower levels in the group treated with Gui-Lin-Tang plus gold than the group treated with Gui-Lin-Tang alone. This was due to the higher rheumatoid activity in patients treated with Gui-Lin-Tang plus gold. Twenty-one patients (61.7%) in Gui-Lin-Tang group and 6 (75%) in Gui-Lin-Tang plus gold group showed improvement. Twenty patients (58.8%) in Gui-Lin-Tang group and 5 (62.5%) in Gui-Lin-Tang plus gold group showed increased grip strength. Twenty-five patients (73.5%) in Gui-Lin-Tang group and 8 (100%) in Gui-Lin-Tang plus gold group showed decreased numbers of painful joints. Eleven (34.3%) in 26 patients treated with Gui-Lin-Tang and 5 (62.5%) in 7 patients treated with Gui-Lin-Tang plus gold showed lower ESR values.

The average values of immunoglobulin were decreased in the group treated with Gui-Lin-Tang alone but not in the group treated with Gui-Lin-Tang plus gold. IgG in eight patients, IgA in 8 patients and IgM in 8 patients were shown lower values in Gui-Lin-Tang group. IgG in 2 patients, IgA in 4 patients and IgM in 3 patients were shown decreased values in Gui-Lin-Tang plus gold group. Even the values of immunoglobulin were changed but most of them were still in normal range.

The improvements of functional capacity were shown in Table 3. Most of the patients in Gui-Lin-Tang group had better functional capacity than those in Gui-Lin-Tang plus gold group before treatment. This was because the patients in the Gui-Lin-Tang group were at the early stage of the disease. The patients in both groups had increased functional capacity after treatment. The roentgenographic progress showed no change in most patients except one patient progressed from stage 2 to stage 3, and another one progressed from stage 1 to stage 2.

Hemoglobin, white count, GOT, GPT, BUN, creatinine and urinalysis were monitored but no toxic reaction was found in either group. There were some adverse side effects but they were

Table 3. Therapeutic classification before and after treatment with Gui-Lin-Tang

		Before treatment (No. of patients)		After treatment (No. of patients)	
		stage	class	stage	class
Gui-Lin-Tang	I	8	23	7	28
	II	22	10	23	6
	III	2	1	2	0
	IV	2	0	2	0
	Total	34	34	34	34
Gui-Lin-Tang & Gold	I	0	0	0	2
	II	3	6	2	4
	III	3	1	4	1
	IV	2	1	2	1
	Total	8	8	8	8

tolerated. Two patients in Gui-Lin-Tang group and 3 in Gui-Lin-Tang plus gold had blurring of vision. Two patients in Gui-Lin-Tang group and 1 in Gui-Lin-Tang plus gold group had dry mouth sensation. One patient had prolonged menstruation, 1 had echymosis and 2 had skin itching in Gui-Lin-Tang treated group. Only one patient had skin rash in Gui-Lin-Tang plus gold group. The skin rash disappeared after the patient was treated with Gui-Lin-Tang without gold (Table 4).

Talbe 4. Adverse reactions to Gui-Lin-Tang treatment

	Gui-Lin-Tang	Gui-Lin-Tang+Gold
Blurring vision	2	3
Dry mouth	2	1
Prolonged menstruation	1	0
Echymosis	1	0
Itching	2	0
Skin rash	0	1
Total	8	5

DISCUSSION

Gui-Zhi-Tang, containing Cinnamomi Ramulus, Paeoniae Radix, Zingiberis Rhizoma, Zizyphi Fructus and Glycyrrhizae Radix has been administered as an antipyretics or antispasmodus by Chinese herb doctor since ancient time.

Modified formula of Gui-Zhi-Tang with prepared Fu Zi is used to treat windphobia, spasm which resulted in inability to stretch and contract the extremities, and other symptoms of chronic articular rheumatism.

Each component of Gui-Zhi-Tang has its own effect. Cinnamomi Ramulus, containing cinnamic aldehyde, is used as an antipyretics or diuretics. Paeoniae Radix, containing paeoniflorin, has antispasmodic, analgesic and circulatory enhancing effects. Zingiberis Rhizoma, containing zingiberol, enhances blood circulation and inhibit adjuvant arthritis in mice. Zizyphi Fructus, containing protein, sugar and vitamins, is a nutrient and a tonic. Glycyrrhizae Radix, contining glycyrrhizin, has antitoxic and anti-inflammatory effects but it may cause edema and hypertension if used too long. Glycyrrhizin can further decompose to glycyrrhetic acid and glucuronic acid in the body. Glycyrrhetic acid has an effect to lower the basal metabolic rate. Aconiti Tuber, containing hypaconitine and aconitine, has vasodilatation, anti-inflammatory and cardiotonic effects but overdose may result in ventricular fibrillation. The efffect of the formula is the sum effect of these component drugs.

Gui-Lin-Tang used in this study is adding Atractylodis Rhizoma and Poria to modified Gui-Zhi-Tang with Fu Zi to enhance the diuretic effect for removing the uric acid. Kano *et al.*, reported the inhibition of adjuvant arthritis by Gui-Zhi-Tang[7]. Walksman *et al.*, speculated that adjuvant arthritis was caused by cell-mediated or delayed immune reacion[10]. From the results

of this study, it seems that the analgesic and edema inhibition of Gui-Lin-Tang is related to immune regulatory function in the body, and the Gui-Lin-Tang has the effect to inhibit immune function.

There was no summation effect after treating the patient by adding Gui-Lin-Tang in addition to gold. Further study is necessary to elucidate the cause.

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中 文 摘 要

桂苓湯對於類風濕性關節炎療效的研究

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72 位服用桂苓湯之確定的或典型的類風濕性關節炎患者中，44 位(女 33 人，男 11 人)完成療效研究，其中 34 位僅用桂苓湯，另外 10 位則以桂苓湯配合金或 D-penicillamine 治療。全部患者平均服藥 77.2 天，有 12 人(27.2%)明顯改善，22 人(50%)稍微改善，10 人(22.8%)無效。61.5%只用桂苓湯治療的患者其 IgG, IgA 及 IgM 值降低。